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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,870	06/13/2005	Anders Oehrvik	1031-PCT-US	5236

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EXAMINER	
BULL, CHRISTOPHER	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/522,870	OEHRVIK ET AL.	
	Examiner	Art Unit	
	Christopher Bull	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 Jan 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *26 Jan 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Abbreviations used:	Type
AZT = 3'-azido-3'-deoxythymidine	TK1 Substrate
AZT-MP = 3'-azido-3'-deoxythymidine-5'-monophosphate	TK1 Product
TK1 = thymidine kinase 1	Enzyme
ELISA = enzyme linked immunosorbent assay	Multiwell Plate Assay
DTE = dithioerythritol	Reducing Agent
DTT = dithiothreitol	Reducing Agent
β-ME = β-mercaptoethanol	Reducing Agent
ATP = adenosine-5'-triphosphate	Phosphate Donor
HEPES = N'-hydroxyethyl-piperazine-N-ethyl-2-sulphonic acid	Buffer
Tris = tris(hydroxymethyl)methylamine	Buffer

Claims 1-20 have Unity of Invention and are presented for examination on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 2, the phrase "R is selected from but not limited to the group consisting of " renders the claim vague and indefinite because it is unclear whether the

limitations following the phrase are part of the claimed invention. It would appear that the definition of R is in no way limited to the group that follows and that R could be anything (except for OH as recited by a limitation to 3'-deoxythymidine in the second line of the claim). Therefore there is no purpose to the following group structure and the Markush language, which is appropriate only in reciting a closed set of choices. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-3, and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Furman et al. (1986 Proc Nat Acad Sci 83, 8333-8337, hereinafter Furman).

Furman teach an assay for TK1 that involved tritium labeled AZT (Chemicals page 8334) and measurement of radioactivity in the phosphorylated product (Assays page 8336). Cellular samples of TK1 was used as enzyme, and activity towards AZT was measured as AZT-MP (Fig 1 page 8335). AZT is a 3'-derivatives of thymidine and AZT-MP is a 5'-phosphorylated-3'-derivatives of thymidine. The phosphate donor was ATP, intracellular or added (page 8334), and the cells were incubated in an RPMI cell culture medium (page 21). A cell culture medium is an appropriate buffer, in the absence of evidence to the contrary.

Claim 1 recites a method comprising steps of: reacting a sample [the cells of Furman] with a substrate for a TK1 [AZT], which substrate is a 3'-derivative of thymidine [AZT] in the presence of a phosphate donor [ATP] and a buffer system [cell culture medium]; and determining the amount of 5'-phosphorylated 3'derivative of thymidine formed [AZT-MP], said amount being related to TK1 activity [page 8335 right side]. Shown above in [ ] are the relevant portions of Furman that read on the claim.

Claim 2 recites the method of claim 1 with no further limitations, since formula I is a 3'-derivative of thymidine and the Markush group is improper by being unlimited.

Claim 3 adds that AZT be substrate and AZT-MP be product [as done].

Claim 9 requires substrate above 0.4 μM [AZT 100 μM page 8334 upper right].

Claim 10 requires phosphate donor between 0.1-10 mM [ATP 5 mM page 8334 upper right].

Accordingly, the reference is deemed to anticipate the matter of Claims 1-3, and 9-10.

Claim 1-4, 6, 9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Goujon et al. (1998 J Immun Meth 218, 19-30, hereinafter Goujon).

Goujon teach an immunological (page 26) ELISA based method for determining intracellular levels of AZT-MP (section 3 pages 25-27). Cells were provided with AZT at different concentrations and intracellular AZT-MP measured (Figure 3 page 26). AZT is a 3'-derivative of thymidine, and AZT-MP is a 5'-phosphorylated 3'derivative of thymidine (abbrs page 19) that is made by thymidine kinase (page 20 middle of left and right columns). The phosphate donor was intracellular ATP, and the cells were

incubated in an RPMI cell culture medium (page 21). A cell culture medium is an appropriate buffer, in the absence of evidence to the contrary. Cells were tested either quiescent or activated, whereupon the TK1 level is dramatically increased (page 24-25).

Claim 1 recites a method comprising steps of: reacting a sample [the cells of Guijon] with a substrate for a TK1 [AZT], which substrate is a 3'-derivative of thymidine [AZT] in the presence of a phosphate donor [intracellular ATP] and a buffer system [cell culture medium]; and determining the amount of 5'-phosphorylated 3'derivative of thymidine formed [AZT-MP], said amount being related to TK1 activity [note the 100 fold increase activated vs resting in Figure 3]. Shown above in [ ] are the relevant portions of Goujon that read on the claim.

Claim 2 recites the method of claim 1 with no further limitations, since formula I is a 3'-derivative of thymidine and the Markush group is improper by being unlimited.

Claim 3 adds that AZT is the substrate and AZT-MP is the product [as done].

Claim 4 requires that the product be determined by an immunological method by complexing with the 5'-phosphorylated 3'derivative of thymidine [the AZT-MP ELISA].

Claim 6 requires that detection by an enzyme linked immunosorbent assay [the AZT-MP ELISA].

Claim 9 requires a substrate level above 0.4 μM [Fig 3 covers 0.01 to 10 μM].

Claim 11 recites the same steps as Claim 1 for monitoring a condition [Fig 3 relates the high AZT-MP level in these human cells to a condition: activated cells].

Accordingly, the reference is deemed to anticipate the matter of Claims 1-4, 6, 9, and 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 9-17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goujon in view of O'Neill (US 5,698,409 issued 16 Dec 1997).

The teachings of Goujon have been discussed above and are applied as before to Claims 1-4, 6, 9 and 11. Goujon also beneficially state (page 27 top left paragraph): "The assay also proved suitable for kinetic measurements of the intracellular production of AZT-MP since it allowed detection of intracellular AZT-MP from 30 minutes after the cells were in contact with the drug (Fig 4)." They further beneficially state (page 20

lower right paragraph) that "So far, the determination of intracellular dideoxynucleotides phosphates has been mainly achieved by using radiolabelled drugs in combination with HPLC techniques to separate the different nucleotides... This approach, which was essential for measuring dideoxynucleotides in *in vitro* cell systems cannot be applied tin clinical studies." Goujon further beneficially state (page 28 left midway) that "The use of a solid-phase separation (microtiter plates) and a non-isotopic tracer makes it suitable for routine analysis in any clinical laboratory. An individual technician can assay more than 100 samples in a single day..."

Goujon did not teach a buffer comprising DTE, ATP, $MgCl_2$, and (HEPES or Tris) with a pH between 6.5 and 8, nor diagnosing or monitoring various cancers, diseases or progressions thereof.

O'Neill teach methods of purifying TK1, inducing monoclonal antibodies to active TK1, and methods measuring active TK1 protein for the diagnosis and prediction of recurrence of cancer (abstract). O'Neill further confirms the correlation between level of active TK1 and various cancers including breast, gastrointestinal and prostate cancers (Table 4), and utility in predicting the recurrence (Col 19-20) of cancers including leukemia (Col 20 lines 43-48). O'Neill also teach (Col 21) methods and kits for performing TK1 activity assays based on active TK1 protein detection, and (Example 1, Col 9 lines 59-65) assay mixture containing Tris-Cl pH 7.8, 2 mM $MgCl_2$, 5 mM β-ME and 4 mM ATP. The β-ME must be omitted as it reacts with Ellman's reagent directly and would otherwise interfere. O'Neill does state that (Col 20 lines 60-63) that "Because the anti-AcTK1 antibody detects on the active 100 kDa form of TK1, it can be used in

place of the routine radioactive thymidine incorporation assay to evaluate specifically TK1 activity." Although this statement might appear to teach away from monitoring enzyme activity directly, it was directed at the only accepted methods of the time all of which involved handling radioactive materials.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to employ the methods and kits for an ELISA test of TK1 activity for cancer and disease diagnosis and monitoring, with the non-radioactive enzyme activity assay using AZT-MP via the instantly claimed steps, because Goujon teach that it is within the ordinary skill in the art to directly monitor TK1 activity using an ELISA specific to AZT-MP and O'Neill teaches that it is within the ordinary skill in the art to use certain buffers for measuring TK1 activity, and to apply the results to cancer and disease diagnosis and monitoring, and to supply kits to perform the assay methods.

One would have been motivated to do so for the expected benefit of directly monitoring TK1 activity with a non-radioactive assay capable of high throughput, as taught by Goujon and O'Neill.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

With regard to Claim 10 which recites a phosphate donor concentration between 0.1 ands 10 mM, the combination [O'Neill Example 1 ATP = 4 mM) reads on the claim.

With regard to Claim 12 where the method is for monitoring or diagnosing cancer, the combination [O'Neill Example 12] reads on the claim.

With regard to Claim 13 where the method is for monitoring or diagnosing various cancer, the combination [O'Neill Example 12] reads on the claim.

With regard to Claim 14 where the condition is a high risk of disease progression, the combination [O'Neill Col 20 line 45] reads on the claim.

With regard to Claim 15 where the method is for diagnosing or monitoring therapeutic treatment of disease, the combination [O'Neill Col 20 lines 53-59] reads on the claim.

With regard to Claim 16-17 which recite a kit for diagnosis or monitoring, with AZT-MP detection, the combination includes the kits of O'Neill [O'Neill Col 21] with the high throughput clinical assays envisaged by Goujon [Goujon page 28 left midway] reads on the claim.

With regard to Claim 19 which further recites a kit wherein the reagents are packed together in a container, the combination reads on the claim as described above for Claim 16, recognizing that claim 19 merely describes the basic idea of a kit.

Claims 1-6, 9-17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goujon and O'Neill as applied to claims 1-4, 6, 9-17 and 19 above, and further in view of Sabelle et al. (5 Apr 2002 JACS 124, 4874-4880, hereinafter Sabelle).

Claim 5 recites using chemiluminescence in an immunological method for TK1 activity.

The teachings of Goujon and O'Neill have been discussed above and are applied as before to Claims 1-4, 6, 9-17 and 19. O'Neill also beneficially allow in their ELISA for "another detectable marker such as a fluorescent dye, radioactive isotope, or the like." (Col 21 line 30-33). Goujon also beneficially teach an AZT-MP assay by ELISA using acetylcholinesterase as the detection enzyme coupled to Ellman's reagent (page 24).

The combination of Goujon and O'Neill did not teach using chemiluminescence.

Sabelle teach using chemiluminescence to detect acetylcholinesterase activity in an ELISA format (page 4880). Sabelle also beneficially state that this assay is tenfold more sensitive than Ellman's reagent (page 4879).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to employ a chemiluminescence assay with the non-radioactive TK1 activity assay detecting AZT-MP using acetylcholinesterase via the instantly claimed steps, because Sabelle teach that using chemiluminescence to detect ELISA acetylcholinesterase activity is better than using Ellman's reagent and Goujon teach that it is within the ordinary skill in the art to directly monitor TK1 activity in an ELISA specific to AZT-MP that detects acetylcholinesterase activity using Ellman's reagent.

One would have been motivated to do so for the expected benefit of more sensitive TK1 activity non-radioactive ELISA assay capable of high throughput, as taught by Sabelle.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-4, 6-7, 9-17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goujon and O'Neill as applied to claims 1-4, 6, 9-17 and 19 above, and further in view of Karlstrom et al. (1990 Mol Cell Biochem 92, 23-35, hereinafter Karlstrom).

Claim 7 is drawn to the method wherein the buffer comprises DTE, ATP, $MgCl_2$ and (HEPES or Tris) with pH between 6.5 to 8.0.

The teachings of Goujon and O'Neill have been discussed above and are applied as before to Claims 1-4, 6, 9-17 and 19, except that the detection enzyme (e.g., peroxidase) to be used for the ELISA is taken from O'Neill, instead of the acetylcholinesterase of Goujon. O'Neill also beneficially teach detecting their ELISA assay using peroxidase and tetramethylbenzidine (Col 14 lines 6-15). O'Neill further beneficially teach using as a thiol reducing agent β-mercaptoethanol (Col 9 lines 65-65) in an assay buffer of 0.02 M tris-Cl pH 7.8, 5 mM β-ME, 4 mM ATP, and 2 mM $MgCl_2$.

The previous combination of Goujon and O'Neill did not teach using DTE as the thiol reducing agent, because thiol reducing agents interfere with Ellman's reagent.

Karlstrom teach using DTE as thiol reducing agent to increase stability of TK1 in assays (Figure 5 page 32). Karlstrom also teach using as buffer HEPES pH 7.4, with DTE, 4 mM ATP, and 2 mM $MgCl_2$.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to employ a buffer that comprises at least DTE, ATP, $MgCl_2$, and (HEPES or Tris) via the instantly claimed steps, because Karlstrom teach that it is within the ordinary skill in the art to use DTE and HEPES in buffers in TK1 assays and the combination of Goujon and O'Neill teach that it is within the ordinary skill in the art to use β-ME and Tris in buffers in an assay (not based on detection with Ellman's reagent) to directly monitor TK1 activity in an ELISA specific to AZT-MP with coupling to peroxidase activity detected using tetramethylbenzidine.

One would have been motivated to do so for the expected benefit of improved TK1 stability in the non-radioactive ELISA assay capable of high throughput, as taught by combination of Goujon and O'Neill.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-4, 6 and 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goujon and O'Neill as applied to claims 1-4, 6, 9-17 and 19 above, and further in view of Stefanovic et al. (1988 Ren Physiol Biochem 11(1-2), 89-102, hereinafter Stefanovic).

Claim 8 is drawn to the method wherein the buffer comprises UMP. Claims 18 and 20 are drawn to versions of the kit comprising UMP.

The teachings of Goujon and O'Neill have been discussed above and are applied as before to Claims 1-4, 6, 9-17 and 19 (i.e., ELISA detection of AZT-MP by Ellman's reagent).

The previous combination of Goujon and O'Neill did not teach using UMP to inhibit phosphatases.

Stefanovic teach using UMP to inhibit phosphatases (Abstract). Stefanovic investigated ecto-5'-nucleotidases in cultured rat cells before and after disruption, and found that 5'-UMP was strictly a competitive inhibitor of this membrane bound phosphatase activity. Lysed cell membranes would necessarily be present in the claimed assay.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to employ UMP as an inhibitor of phosphatases in an assay for a nucleotide phosphate such as AZT-MP via the instantly claimed steps, because Stefanovic teach that it is within the ordinary skill in the art to use UMP to inhibit phosphatases and the combination of Goujon and O'Neill teach that it is within the ordinary skill in the art to directly monitor TK1 activity in an ELISA specific to AZT-MP by coupling to acetylcholinesterase activity detected using Ellman's reagent.

One would have been motivated to do so for the expected benefit of improved sensitivity in the non-radioactive ELISA assay for TK1, as taught by combination of Goujon and O'Neill, since nucleotidase activity could otherwise hydrolyze AZT-MP back to AZT and reduce assay response.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

With regard to Claim 18 where the kit includes UMP, the combination with Stefanovic adds the UMP to the kits of Goujon and O'Neill and so reads on the claim.

With regard to Claim 20 where the kit includes UMP, the combination with Stefanovic adds the UMP to the kits of Goujon and O'Neill and so reads on the claim.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Fridland et al. (1990 in Molec Pharm 37, 665-670) HPLC monitoring of TK1 activity in cells following AZT-MP.

Peter et al. (1996 in Clin Pharmcol Therapy 60, 168-176) HPLC/immunoassay monitoring of TK1 activity in cells following AZT-MP.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Bull whose telephone number is (571) 272-1327. The examiner can normally be reached on 7:30-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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